Steroidal Sapogenins. XXX
Stereochemistry of the Side Chain

A number of workers have recently investigated the stereochemistry of the stereoidal sapogenin side chain[1]. The fact that naturally occurring sapogenins have isomerism at C_{25} was established by SCHEER, KOSTIC, and MOSETTIG, and by JAMES[2]. Work at this laboratory[3] has shown that natural sapogenins have the 20α configuration whereas the unnatural 20-isosapogenins (also called ana-[4], cyclopseudo-[5], and neosapogenins[6]) have the 20β orientation. It has also been recently demonstrated that a true equilibrium is established as a result of heating sapogenins with alcoholic HCl[7], sarsasapogenin and smilagenin each giving a mixture containing approximately 20% of the former and 80% of the latter.

[1] I. SCHEER, R. B. KOSTIC, and E. MOSETTIG, J. Amer. Chem. Soc. *75*, 4871 (1953); *77*, 641 (1955). – V. H. T. JAMES, Chem. and Ind. *1953*, 1388. – M. E. WALL, C. R. EDDY, and S. SEROTA, J. Amer. Chem. Soc. *76*, 2849 (1954); *77*, 1230 (1955). – R. K. CALLOW and V. H. T. JAMES, Chem. and Ind. *1954*, 691. – D. H. W. DICKSON *et al.*, Chem. and Ind. *1954*, 692. – D. A. H. TAYLOR, Chem. and Ind. *1954*, 1066. – J. B. ZIEGLER, W. ROSEN, and A. C. SHABICA, J. Amer. Chem. Soc. *76*, 3865 (1954); *77*, 1223 (1955). – M. E. WALL, S. SEROTA, and L. P. WITNAUER, J. Amer. Chem. Soc. *77*, 3086 (1955) (in press). – M. E. WALL and H. A. WALENS, J. Amer. Chem. Soc. *77* (1955) (in press). – M. E. WALL and S. SEROTA (MS. in preparation).

[2] V. H. T. JAMES, Chem. and Ind. *1953*, 1388.

[3] M. E. WALL, C. R. EDDY, and S. SEROTA, J. Amer. Chem. Soc. *76*, 2849 (1954); *77*, 1230 (1955).

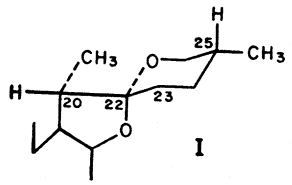
[4] R. K. CALLOW and V. H. T. JAMES, Chem. and Ind. *1954*, 691. – D. H. W. DICKSON *et al.*, Chem. and Ind. *1954*, 692.

[5] D. A. H. TAYLOR, Chem. and Ind. *1954*, 1066.

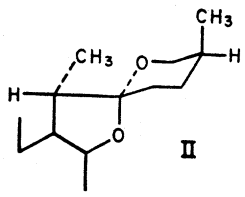
[6] J. B. ZIEGLER, W. ROSEN, and A. C. SHABICA, J. Amer. Chem. Soc. *76*, 3865 (1954); *77*, 1223 (1955).

[7] M. E. WALL, S. SEROTA, and L. P. WITNAUER, J. Amer. Chem. Soc. *77* (1955) (in press).

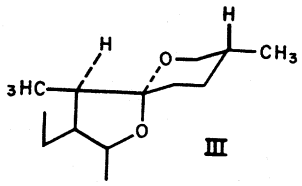
From the foregoing considerations (presented in greater detail in references[1]) the side chain formulation



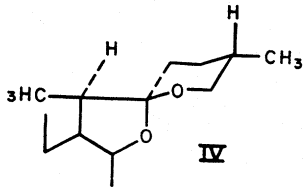
I



II



III



IV

of smilagenin and related 20α, 25D-sapogenins is best represented by I.

Recently, we prepared a number of 20β, 25D- and 20β, 25L-sapogenins[2]. From a comparison of the specific rotations of these sapogenins with their 20α analogues (Table), the author has deduced that formulation II best represents sarsasapogenin and 20α, 25L-sapogenins; formulation III is given to 20-isosmilagenin and related 20β, 25D-sapogenins; and formulation IV best fits 20-isosarsasapogenin and related 20β, 25L-sapogenins.

The basis for the above assignments is the assumption that the highly polar asymmetric center at C_{22} is responsible for the major portion of the observed $[\alpha]_D$ of sapogenins and that the centers at C_{20} and C_{25} have only a

[1] M. E. WALL, C. R. EDDY, and S. SEROTA, J. Amer. Chem. Soc. *76*, 2849 (1954); *77*, 1230 (1955). – D. A. H. TAYLOR, Chem. and Ind. *1954*, 1066. – J. B. ZIEGLER, W. ROSEN, and A. C. SHABICA, J. Amer. Chem. Soc. *76*, 3865 (1954); *77*, 1223 (1955).

[2] M. E. WALL, C. R. EDDY, and S. SEROTA, J. Amer. Chem. Soc. *76*, 2849 (1954); *77*, 1230 (1955). – M. E. WALL and H. A. WALENS, J. Amer. Chem. Soc. *77* (1955) (in press). – M. E. WALL and S. SEROTA (MS. in preparation).

minor effect on $[\alpha]_D$. It follows that any major change in the $[\alpha]_D$ of sapogenins must be ascribed to a change at C_{22}.

Let us examine the data which substantiates this assumption. Columns 1 and 2 of Table give the $[\alpha]_D$ of a number of 20α and 20β pairs known to differ at C_{25} in each series[1]. The $[M]_D$ differences for the 20α series are shown in column 3 and are of obvious low magnitude. Column 4 gives the same data for the 20β series and shows a pronounced dextrorotatory shift of large magnitude. We have shown[2] that the C_{25} configurations of sapogenins of the 20β series are identical to their corresponding 20α analogues. Accordingly, we can rule out C_{25} isomerism as a factor in the pronounced dextrorotatory shift observed in the 20β series since we have demonstrated that corresponding C_{25} differences in the 20α series have little effect on rotation. Similarly we can demonstrate that the C_{20} center exerts only a minor effect. Column 6 shows that a change from 20α to 20β in the 25 D series has an average effect of about + 45 units. Column 5 shows that the same change from 20α to 20β in the 25 L series is of much greater magnitude and of the same order found in column 4 which compares 25 L and 25 D isomers with the same $C_{20}\beta$ configuration.

One must conclude that the great dextrorotatory shift found in passing to the 20β, 25 L series is due to the fact that this group *differs at* C_{22} from its 20β, 25 D; 20α, 25 D; and 20α, 25 L isomers and further that all the other series are *identical at* C_{22}. Furthermore the data supports the view that the highly polar spiroketal C_{22} group is responsible for the major part of the $[\alpha]_D$ values observed with sapogenins. Additional evidence for this view is the fact that whenever the polar spiroketal ring is opened as in the formation of pseudo-, dihydro-, and dihydropseudosapogenins, there is again a pronounced dextro-

[1] I. SCHEER, R. B. KOSTIC, and E. MOSETTIG, J. Amer. Chem. Soc. *75*, 4871 (1953); *77*, 641 (1955). – M. E. WALL, C. R. EDDY, and S. SEROTA, J. Amer. Chem. Soc. *76*, 2849 (1954); *77*, 1230 (1955). – M. E. WALL, S. SEROTA, and L. P. WITNAUER, J. Amer. Chem. Soc. *77*, 3086 (1955) (in press).

[2] M. E. WALL, C. R. EDDY, and S. SEROTA, J. Amer. Chem. Soc. *76*, 2849 (1954); *77*, 1230 (1955). – M. E. WALL, S. SEROTA, and L. P. WITNAUER, J. Amer. Chem. Soc. *77*, 3086 (1955) (in press).

Compound	$[\alpha]_D^{0}$ *		[M_D]** Differences			
	1 20α	*2* 20β	*3* ΔE_1[a]	*4* ΔE_2[b]	*5* ΔE_3[c]	*6* ΔE_4[d]
Sarsasapogenin 25L	− 75	+ 31[1]				
Smilagenin 25D	− 71	− 59[1]	−17	+374	+440	
Markogenin 25L	− 70	+ 13[2]				+ 50
Samogenin 25D	− 74	...	+17	...	+358	
Yamogenin 25L	−129	− 15[2]				...
Diosgenin 25D	−129	−103[2]	0	+364	+473	
		−122[3]				+108
3-Desoxysarsasapogenin. 25L	− 73	+ 37[2]				+ 29
3-Desoxysmilagenin 25D	− 71	− 63[2]	− 8	+400	+444	
3-Desoxytigogenin 25D	− 69	− 59[2]				+ 32
Tigogenin 25D	− 67	− 67[2]				+ 40
						0

* $[\alpha]_D$ of 20α series determined in chloroform, 20β series in dioxane and converted to chloroform basis by adding (−5) to each observed dioxane value.

** $M_D = [\alpha]_D \times$ molecular weight/100

[a] $\Delta E_1 = M_D[(20\alpha,25L)-(20\alpha,25D)]$ [c] $\Delta E_3 = M_D[(20\beta,25L)-(20\alpha,25L)]$

[b] $\Delta E_2 = M_D[(20\beta,25L)-(20\beta,25D)]$ [d] $\Delta E_4 = M_D[(20\beta,25D)-(20\alpha,25D)]$

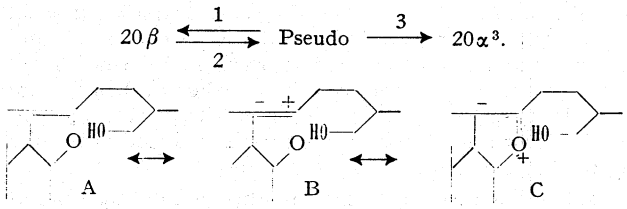
[1] M. E. Wall, C. R. Eddy, and S. Serota, J. Amer. Chem. Soc. *76*, 2849 (1954); *77*, 1230 (1955).

[2] M. E. Wall and H. A. Walens, J. Amer. Chem. Soc. *77* (1955) (in press). – M. E. Wall and S. Serota (MS. in preparation).

[3] J. B. Ziegler, W. Rosen, and A. C. Shabica, J. Amer. Chem. Soc. *76*, 3865 (1954); *77*, 1223 (1955).

rotatory change in the rotation and the observed $[\alpha]_D$ values are generally near zero[1]. Formulation I has been assigned to smilagenin by several research groups[2] and certainly seems reasonable on the basis of information at hand. It follows from the optical rotation data previously cited that sarsasapogenin is II differing from I only at C_{25}; 20-isosmilagenin is III, differing from I only at C_{20}, and 20-isosarsasapogenin is IV differing from I at C_{20}, C_{22}, and C_{25}. The author proposes that sapogenins of groups I, II, III, IV be called respectively 20α, 22*a*, 25D-; 20α, 22*a*, 25L-; 20β, 22*a*, 25D-; and 20β, 22*b*, 25L-sapogenins (G. MUELLER and B. RIEGEL first proposed this nomenclature system).

Finally, let us examine the manner in which the series I–IV could be formed by cyclization of the pseudosapogenins. It is probable that pseudosapogenins exist as resonance stabilized hybrids. In the presence of H^+, cyclization takes place in the sequence:



Assuming cyclization of the planar forms *B* or *C* of pseudosapogenins, there is no longer need to be bound rigidly by the concept of trans ring closures[4]. The nature

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[3] M. E. WALL, C. R. EDDY, and S. SEROTA, J. Amer. Chem. Soc. *76*, 2849 (1954); *77*, 1230 (1955). – R. K. CALLOW and V. H. T. JAMES, Chem. and Ind. *1954*, 691. – D. H. W. DICKSON *et al.*, Chem. and Ind. *1954*, 692.

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of the various isomers which are formed seems to depend entirely on *steric effects*.

Considering first the 20α series, it will be noted that models with C_{22} configuration opposite that of I and II indicate that there would be a strong interaction between the C_{21} methyl and the C_{23} methylene groups. Models show much less interaction between the C_{21} methyl and the smaller oxygen atom as shown in I and II so that these forms have less overall energy and are favored. In the case of II, the interaction of the axial C_{27} methyl with a single hydrogen atom has less effect on the overall energy of the molecule than the C_{21}–C_{23} interactions discussed above.

A different situation occurs in the 20β series. In this case the C_{21} methyl is replaced by a much smaller hydrogen atom, and models show no interaction in either of the two C_{22} possibilities. Under these circumstances steric effects at C_{25} might well determine the direction of ring closure so that in each case the more stable equatorial C_{27} methyl is formed. This would require a *cis* closure in the case of III and a *trans* closure in the case of IV. The foregoing rationalization of the cyclization of pseudosapogenins to give the series I–IV is thus in complete accord with the formulations deduced from the optical rotations of these compounds.

There remains for discussion the infrared spectra of I–IV. Originally, we concluded in agreement with R. N. JONES that the large differences between the infrared spectra of I and II were due to differences in C_{22} configuration[1]. The present evidence renders the above hypothesis untenable. Instead the infrared differences between I and II must be ascribed to the equatorial and axial C_{27} methyl group. The markedly different spectre of III[2]. must be ascribed to the strain produced by the

[1] M. E. WALL, C. R. EDDY, and S. SEROTA, J. Amer. Chem. Soc. *76*, 2849 (1954); *77*, 1230 (1955). – M. E. WALL, C. R. EDDY, M. L. MCCLENNAN, and M. E. KLUMPP, Anal. Chem. *24*, 1337 (1952). – C. R. EDDY, M. E. WALL, and M. K. SCOTT, Ana l Chem. *25*, 266 (1953). – R. N. JONES, E. KATZENELLENBOGEN and K. DOBRINER, J. Amer. Chem. Soc. *75*, 158 (1953).

[2] M. E. WALL, C. R. EDDY, and S. SEROTA, J. Amer. Chem. Soc. *77*, 1230 (1955).

20β configuration, and that of IV both to the 20β and to the difference in C_{22} configuration.

M. E. WALL

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Zusammenfassung

Die optischen Drehungen einiger 20α, 25D; 20α, 25L; 20β, 25D; und 20β, 25-L-Sapogenine wurden bestimmt. Die ersten drei Serien gaben übereinstimmend linksdrehende Werte, aber die letztere Gruppe erwies sich als rechtsdrehend.

Die Struktur der vier Serien der Sapogenine folgte aus der Analyse dieser Befunde. Der mögliche Mechanismus bei der Entstehung dieser Verbindungen aus Pseudosapogeninen wurde besprochen. Die Autoren gelangen zum Schluss, dass sterische Faktoren an C_{20} und C_{25} die Richtung der Ringschliessung beeinflussen.